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EXAMINER	
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1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,237	BLOCK, ANDREAS	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 2/7/07 have been fully considered but they are not persuasive. Claims 1-18 are pending. Claims 13-18 are canceled.

Claims 1-12 are under consideration.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim **1** rejection under 35 U.S.C. 102(a) as being anticipated by **Fitzimons et al,** (Gene Therapy, 8: 1675-1681, 2001) is maintained for the reasons of record mailed 8/8/06.

Applicants argue that the office has not pointed out element by element how Fitzimons describes a vector of identical general structure and orientation. These arguments are not persuasive.

The office action mailed 8/8/06 specifically points out element by element how Fitzimons describes an adenoviral vector, which contains every single structural element embraced by the claim. The office action describes the elements of the insert in a format from a to g. In the instant case claim 1 does not embrace any type of orientation of any structural element of the

insert. The claim embraces a general structure of the insert and Fitzimons anticipates each element embraced by claim 1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, and 5-12 rejection under 35 U.S.C. 102(b) as being anticipated by **Nakagawa et al,** is withdrawn.

Claims 1, and 5-12 rejection under 35 U.S.C. 102(b) as being anticipated by **Strahtee et al,** is withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims **1, 5-12** rejection under 35 U.S.C. 103(a) as being unpatentable over Nakagawa et al, in view of Lode et al, is withdrawn.

Applicant's arguments with respect to claims 1, 5-12, have been considered but are moot in view of the new ground(s) of rejection.

Claims **1-3, 5, 7-12 are** rejected under 35 U.S.C. 103(a) as being unpatentable over **Fitzimons et al,** (Gene Therapy, 8: 1675-1681, 2001) in view of **Nakagawa et al**, (European Journal of Pharmaceutical Sciences, 13: 53-60, 2001).

Fitzsimons teaches a recombinant adeno-associated virus (rAAV) viral vector which contains an insert exhibiting the general structure in which, a) the $TetO_7$ is the heptamerized tetracycline operator; b) TK^+ is the minimal thymidine kinase promoter; c) tTA is a nucleic acid sequence which encodes a fusion protein from the repressor protein inducible by tetracycline and the transcriptional activation domain of the Herpes simplex virus VP16, d) CMV is the minimal cytomegalovirus promoter; e) the transgene is a nucleic acid sequence which codes for a non-viral protein luciferase; f) $intron^1$ is a desired non-encoding nucleic acid sequence insulator with a length of 42 bp; and g) $intron^2$ is a desired non-encoding nucleic acid sequence insulator with a length of 42 bp (p 1675, 2nd column, last paragraph and p 1676, 1st column and figure 1) as is claimed in the instant case. **Fitzsimons** also teaches they have optimized the autoregulated-directional rAAV-based construct for in vitro and in vivo regulation of gene expression by doxocycline and they have demonstrated that rAAV-mediated transfer of reporter genes which can be regulated in vitro and in vivo with extremely low basal expression (p 1675, 1st column, 2nd paragraph). **Fitzsimons** also teaches they have minimized the size of the cassette and decreased the basal leakiness of the system, leading to tight regulation in the rat brain (abstract). Fitzimons differs from the present invention for not teaching said insert is inserted into the viral genome in reverse orientation.

However, at the time of the instant invention Nakagawa teaches a two- and one-component tet system where the insert can be inserted into the adenovirus genome in reverse orientation. **Nakagawa** teaches a recombinant adenovirus vector, which contains the transgene encoding for IL-12 controlled by the tetracycline-regulated expression system (p 55, 2nd column, p 56 1st and 2nd column). Nakagawa teaches the utility of both two-component and one-component systems tetracycline-regulatable adenovirus vectors. Two component-systems utilize one adenovirus vector to express the transgene under the control of the TRE and a minimal promoter, and a second adenovirus vector to express the transactivator, either tTA or rTA, from a constitutive promoter (p 55, 2nd column, p 56 1st column, last paragraph). Furthermore, Nakagawa teaches one component-system, wherein both expression cassettes are incorporated into a single adenovirus vector (p 55, 1st column, last paragraph and 2nd column, 1st paragraph and reference by incorporation). Nakagawa also teaches that, the tetracycline-sensitive one component system incorporate both expression cassettes into a single adenovirus vector, wherein the transgene is a nucleic acid sequence encoding the interleukin-12 transgene as claimed in the instant application, (claim 5). Nakagawa also teaches that, the tetracycline-sensitive one component system incorporate both expression cassettes into a single adenovirus vector, wherein the insert is inserted into the E1/E3-deleted backbone of Ad5 [reference by incorporation, (Corti et al, 1999), p 55, 2nd column, 1st sentence] as claimed in the instant application, (claim 8). Nakagawa also teaches that the tet-on system a "reverse" transacivator (rTA) with the opposite properties of tTA binds to the TRE and activates transcription only in the presence of

tetracycline derivatives like doxocycline (p 54, 2nd column, last paragraph). Nakagawa teaches this tet adenovirus system provides new opportunities and improved safety for gene therapy applications in humans. As such Nakagawa provides sufficient motivation for one of ordinary skill in the art to excise the IL-12 insert from the Nakagawa vector and insert it into the viral vector of Fritzimons for gene therapy applications.

Accordingly, in view of the teachings of Nakagawa et al, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the rAAV vector of Fritzimons and insert the IL-12 insert of tetracycline--regulatable technology of **Nakagawa** for gene therapy in a rat brain with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification since Nakagawa teaches the temporal control of exogenous gene expression is essential for IL-12 gene therapy and the improvements to the tet system have resulted in new tTA and rtTA transactivators that are tolerated at higher intracellular concentrations.

Thus, the claimed invention as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Claims **1, 5-7 are** rejected under 35 U.S.C. 103(a) as being unpatentable over **Fitzimons et al,** (Gene Therapy, 8: 1675-1681, 2001) in view of **Lode et al**, (European Journal of Pharmaceutical Sciences, 13: 53-60, 2001).

Fitzsimons teaches a recombinant adeno-associated virus (rAAV) viral vector which contains an insert exhibiting the general structure in which, a) the $TetO_7$ is the

heptamerized tetracycline operator; b) TK^+ is the minimal thymidine kinase promoter; c) tTA is a nucleic acid sequence which encodes a fusion protein from the repressor protein inducible by tetracycline and the transcriptional activation domain of the Herpes simplex virus VP16, d) CMV is the minimal cytomegalovirus promoter; e) the transgene is a nucleic acid sequence which codes for a non-viral protein luciferase; f) $intron^1$ is a desired non-encoding nucleic acid sequence insulator with a length of 42 bp; and g) $intron^2$ is a desired non-encoding nucleic acid sequence insulator with a length of 42 bp (p 1675, 2nd column, last paragraph and p 1676, 1st column and figure 1) as is claimed in the instant case. **Fitzsimons** also teaches they have optimized the autoregulated-directional rAAV-based construct for in vitro and in vivo regulation of gene expression by doxocycline and they have demonstrated that rAAV-mediated transfer of reporter genes which can be regulated in vitro and in vivo with extremely low basal expression (p 1675, 1st column, 2nd paragraph). **Fitzsimons** also teaches they have minimized the size of the cassette and decreased the basal leakiness of the system, leading to tight regulation in the rat brain (abstract). Fitzimons differs from the present invention for not teaching said IL-12 is a single chain IL-12.

However at the time of the instant invention Lode et al, teaches a single chain IL-12 fusion protein induces T cell dependent protective immunity in a syngeneic model of murine neuroblastoma. Lode teaches the single chain IL-12 fusion protein induces a T cell mediated immunity that completely protects mice from challenge with the wild type tumor cells as indicated by the complete absence of liver and bone marrow metastases in a novel syngeneic model of neuroblastoma (p 2475, 2nd column). Lode teaches the

poor immunogenicity of this model clearly demonstrates the feasibility of efficient gene therapy with a single chain IL-12 fusion protein.

Accordingly, in view of the teachings of Lode et al, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the rAAV vector of Fritzimons and insert the single chain IL-12 for gene therapy. One of ordinary skill in the art would have been sufficiently motivated to make such a modification since Fitzimons teaches they have optimized the autoregulated-directional rAAV-based construct for in vitro and in vivo regulation of gene expression by doxocycline and they have demonstrated that rAAV-mediated transfer of reporter genes which can be regulated in vitro and in vivo with extremely low basal expression.

Thus, the claimed invention as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims **1-4, 9-12** remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim **4** is vague and indefinite because in the specification does not describe the use of a lac repressor and particularly point out and distinctly claim the subject matter which

applicant regards as the invention. The specification does not clearly set forth the metes and bounds of the lac repressor. .

Claim **1 remains** vague and indefinite because it recites the phrase "exhibiting the general structure".

Applicants argue in view of the specification, which discloses in paragraphs [8]-[39] of the published application what is encompassed by the general structure, accordingly this phrase is submitted to be sufficiently clear and definite. These arguments are not persuasive because in paragraphs 8-39 is described the cloning techniques for the generation of VLP RNA and the method of the invention can be used for gene therapy. However, the specification has no exhibition of a specific general structure. It is not clear as to whether the term "exhibiting" is used in reference to the general structure of the recombinant viral vector in reference to the general structure of the transgene or in reference to the order of the transactivator and the transgene or in reference to the structure and function of the insert. Further, term "general" fails to set forth how similar or different the claimed vector has to be from that iterated in the claim.

Claim **2 remains** vague because it recites the term "reverse". The claim should state what "reverse orientation" is compared to. Which direction is reverse, which direction is regular.

Applicants argue the recited phrase itself, which recites the insert "is inserted into the viral genome in reverse orientation" clearly communicates to the skilled person the viral vector genome is the point of reference. These arguments are not persuasive because each viral vector genome has various points of reference for the insertion of an insert.

The rejection of claims 2-9 as being vague is withdrawn.

Claim **3 remains** vague because it recites the term "inverted".

Applicants argue the recited phrase itself, which is "wherein the position of tTA and transgene are inverted in the insert" makes clear the two elements are inverted vis-à-vis each

other. These arguments are not persuasive because the claim as such does not describe the point of reference to each other or to a reference point in the vector.

Claim **9 and 10** are indefinite because it recites the phrase nucleic acid sequence "represented" is withdrawn. .

Conclusion

No claim is allowed.

Applicants argue they have amended the claims to address this issue. These arguments are not persuasive because applicants have not amended the claims accordingly.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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